

Peer Review File

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Comment 1: Major concern is that differences in the population characteristics between both treatment groups could be the cause of their different response. Differences in some known risk factors for pneumonitis as smoking and lung size were discussed by the authors. However, some other risk factors should be reported and discussed as well: left vs right lung tumour side and lobe location have previously been shown to influence lung damage quantification on CT (e.g. Defraene et al. Radiother Oncol 2017). This regional information has to be reported and its potential influence studied and acknowledged.

Reply 1: Thanks for your suggestion. We had made some changes in table 1 and discussed in p.17 line 328-335

Changes in the text: Secondly, Defraene et al (27) reported the location of tumor could influence lung damage quantification on CT. But our study did not find significant differences of tumor location between two groups ($p=0.276$). Our research only included patients with small size of tumor treated with SBRT. The lower or upper lobe may not be an independent prognostic factor of density change. Most of the tumors location from the included patients were located in the upper or middle lobe. We got insufficient statistical power to analyze the effect of lower lobe on tumor density due to the limited sample size.

Comment 2: Regarding the lung function assessment comparing matched pairs of patients (Table 4), it is unclear what was exactly the result of this analysis, as no qualitative or quantitative result is presented in the results section.

Reply 2: Your suggestions are very helpful for our paper. So, we have made some changes in p.14 line 258-263 and added some data in table 4. The assessment was subjectively made by at least one radiologist and treating physician independently. It shows insignificant difference between two groups ($p>0.05$).

Changes in the text: The details of the lung function assessment comparing matched pairs of patients was shown in table 4. There were no significant differences between two groups ($p > 0.05$). Figure 1a and 1d shows the ventilation maps of two representative cases.

Comment 3: p.7 line 135 Please add the dose calculation algorithm used?

Reply 3: We had made changes in p.8 line 128-131

Changes in the text: Each SBRT plan was delivered with 9 to 11-field intensity-modulated radiotherapy (IMRT). The dose calculation was done with collapsed cone convolution algorithm (CCC) (Pinnacle, Philips Medical Systems, Milpitas, CA).

Comment 4: p.7 line 136 Was the rigid registration between pre- and post-treatment CT based on bony anatomy or on the lung tumor structure itself?

Reply 4: We had made changes in p.8 line 131-133.

Changes in the text: The pre-SBRT planning CT and post-SBRT CT were rigidly registered based on both bony anatomy and tumor structure. (Eclipse, Varian Medical Systems, Palo Alto, CA).

Comment 5: p.9 line 178 This should refer to equation 3 instead of 4?

Reply 5: We had made changes in p.10 line 174-175.

Changes in the text: NTCP(D_i) is the probability calculated by Eq. (3) for $\Delta\text{HU} \geq 200$ HU at point i .

Comment 6: p.11 line 231 “The maximum difference of HU values corresponded to 168 Gy BED”. It is unclear what this means, how can a HU difference be expressed in Gy?

Reply 6: We had made changes in p.13 line 234-235.

Changes in the text: The maximum difference of ΔHU value between the two groups got at the BED dose of 168 Gy.

Comment 7: p.12 line 244 The m values (steepness parameters) of the dose response curves of both groups are similar (0.48 and 0.49), however, it is stated further (and also in the abstract) that the parameters m are significantly different, which seems to be the case from Figure 1B. How can the m values than be nearly identical?

Reply 7: We had made changes in p.13 line 248-249

Changes in the text: The difference of TD_{50} between the groups was statistically significant ($p < 0.001$)

Comment 8: p.15 line 319 “all SBRT patients were smokers”: from Table 1 it seems there were 5 non-smokers? There is also discrepancy between the text and Table 1 on smoking rate in the TKI group.

Reply 8: We had made changes in p.17 line 323-325.

Changes in the text: Most of patients in the TKI-SBRT group were stage III/IV adenocarcinomas and non-smokers, while majority of patients treated with SBRT alone were male, smokers, and stage I/II disease.

Comment 9: Figure 1: The caption states that row B shows a SBRT alone patient. However, this patient seems to have more delta HU than the one in row A?

Reply 9: We had made changes in figure 1 and text (p.12 line 223-232, p.24 line 461-464).

Changes in the text:

p.12 line 223-232: Patient 1 and 2 displayed in figure 1 were two representative examples from SBRT alone group and TKI+SBRT group respectively. They were matched in gender, smoking status, tumor primary size and location, dose prescription and lung volume. Figure 1a, 1b and 1c for patient 1 showed a pre-treatment lung ventilation map, pre- and post-treatment CT scans with SBRT dose distributions, respectively. Figure 1d, 1e and 1f was the corresponding examples for patient 2. As shown in figure 1, no remarkable differences between two patients were observed in lung ventilation and CT scans before treatment. However, patient 2 got more significant HU changes in CT scans at 3 months after the end of treatment.

p.24 line 461-464: A pre-treatment lung ventilation map (a), a pre- and 3 months post treatment CT scan with SBRT dose distribution (b and c) for the patient 1 treated with SBRT alone; A pre-treatment lung ventilation map (d), a pre- and 3 months post treatment CT scan with SBRT dose distribution (e and f) for the patient 2 treated with EGFR-TKI plus SBRT.

Comment 10: Figure 2A What could be the reason for the negative delta HU values observed at the lowest lung doses?

Reply 10: We suppose that the following causes lead to the result. First, patients had taken enhanced scan before treatment, but the following CT scans were unenhanced. Second, the functional compensation of unirradiated lung may increase to make up the lesion of irradiated lung.

Comment 11: The caption states that SBRT alone have diamond points while that is the high response curve?

Reply 11: We had made changes in p.24 line 471-472.

Changes in the text: Figure 2A shows the dose-response curve (A) between SBRT alone (square point) and TKI+SBRT groups (diamond point).

Comment 12: Table 2 All patients seem to have at least grade 1 pneumonitis: was this a requirement for having a follow-up CT at 3 months?

Reply 12: We concerned about the acute radiation pneumonitis here. The effect at 3 months has been described as the peak of the early phase and is strongly correlated to the late effect just as Defraene reported. (e.g. Defraene et al. Radiother Oncol 2015)